REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

Claims 8-19, 25-29, 31-35, 38, 40-45, and 47-51 are pending. Applicants note that the Office Action Summary does not indicate that claim 38 was pending; however, Applicants note that this claim is pending, as submitted January 5, 2001. By the foregoing amendment, claims 16, 26-28, 32-34, 42-44, and 50 have been canceled without prejudice or disclaimer of the subject matter recited therein. Claims 8, 12, 14, 15, 18, 19, 25, 29, 31, 35, 40, 45, 48, and 49 have been amended to further clarify Applicants' invention. Support for the amendments can be found throughout the specification, at least at page 4, lines 4-9, page 7, lines 20-36, and Examples 1, 2, and 3. Applicants reserve the right to pursue the deleted subject matter in subsequent continuation and/or divisional applications. No new matter has been added.

I. Rejections under 35 U.S.C. § 112, first paragraph

Claims 8-13, 16-19, 25-27, 31-33, 38, 40-43, 47-48 and 51 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. More specifically, the Examiner contends that, apart from the disclosed sequences of the avian REV type A virus, the specification fails to disclose a representative number of species of nucleotide sequences isolated from the 5' leader of a broad genus of reticuloendotheliosis viruses that possess IRES or encapsidation activities. Applicants respectfully traverse this rejection.

However, in order to expedite prosecution in the subject application and without acquiescing to the rejection, Applicants have amended claims 8 and 25 to recite an avian

reticuloendotheliosis virus of type A (REV-A), and amended claims 8 and 25 to remove "or from the DNA equivalent of said genomic RNA, wherein said nucleotide sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation codon of the gag gene". Instead, the claims as amended recite "wherein said nucleotide sequence comprises at least the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 452 and ending at nucleotide 578 or the DNA equivalent of said portion in which U nucleotides are replaced by T nucleotides".

Further, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claim 31 to recite that the REV-A sequence allowing encapsidation of a retrovirus or a retroviral vector comprising at least the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 265 and ending at nucleotide 578 or the DNA equivalent of said portion in which U nucleotides are replaced by T nucleotides.

In view of the above amendments, Applicants have canceled claims 26-28, 32-34, and 42-44 without prejudice or disclaimer of the subject matter recited therein.

Claims 8-19, 25-28, 31-35, 38, 40-45 and 47-51 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. More specifically, the Examiner contends that the specification does not enable the make and use of any nucleotide sequence isolated from the 5' end of the genomic RNA of a reticuloendotheliosis virus (REV) or from the DNA equivalent of said genomic RNA. Applicants respectfully traverse this rejection.

As described above, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claims 8 and 25 to recite an avian reticuloendotheliosis virus of type A (REV-A), and amended claims 8 and 25 to remove "or from the DNA equivalent of said genomic RNA, wherein said nucleotide

sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation codon of the gag gene". As amended herein, the claims recite "wherein said nucleotide sequence comprises at least the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 452 and ending at nucleotide 578 or the DNA equivalent of said portion in which U nucleotides are replaced by T nucleotides". Applicants have amended claim 31 to recite that the REV-A sequence allowing encapsidation of a retrovirus or a retroviral vector comprises at least the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 265 and ending at nucleotide 578 or the DNA equivalent of said portion in which U nucleotides are replaced by T nucleotides.

Applicants submit that the specification provides an enabling disclosure of the presently claimed invention. Undue experimentation is not required because the working examples provide sufficient detail to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. In addition, as described above, Applicants have amended the claims. The Official Action states that it would require undue experimentation for a skilled artisan to make and use the instant broadly claimed invention. It respectfully is submitted that the pending claims should be found to be enabled and allowable.

The specification provides a detailed explanation of how vectors using various species of REV-A sequences can be constructed (see, *e.g.* Examples 1 and 2 and Figures 1 to 3) and used to express one or more genes of interest or to package retroviral genomes into retroviral capsids (see, *e.g.* Examples 2 and 3).

Example 1 describes *in vitro* translation assays performed from RNAs synthesized from either monocistronic or dicistronic beta-galactosidase-expressing plasmid vectors containing the full length REV-A sequence disclosed in SEQ ID NO: 2 (1-578; monocistronic pREV CB-95 and dicistronic pREV CB-54), or shorter versions thereof (i) 265-578 (monocistronic pREV CG-55 and dicistronic pREV CB-55), (ii) 452-578 (monocistronic pREV

CG-56 and dicistronic pREV CG-58) and (iii) 1-578 deleted for sequence 268 to 452 (monocistronic pREV CG-54 and dicistronic pREV CG-52). It is emphasized that the translation of the beta-galactosidase product is dependent of an IRES activity both in non capped monocistronic RNAs and in a dicistronic context. As expected, the presence of the REV-A sequences does not affect the cap-dependent translation (*i e.* beta-galactosidase expression is detected from all capped monocistronic RNAs even when the REV-A sequence is non functional such as in pREV CG-53 in which REV-A 1-578 sequences are inserted in reverse orientation). In marked constrast, when using non capped RNAs, beta galactosidase translation could not be detected from the pREV CG-53 control whereas it was as efficient as that obtained from the capped RNAs when using the constructs containing REV-A sequences in sense orientation. These results illustrate that all the REV-A sequences tested contained in the 1-578 fragment can efficiently initiate the translation of a downstream gene in a cap-independent manner (see page 25 lines 8-17), and that the REV-A sequences contained in the 1-578 fragment (*e.g.* 1-578, 265-578, 452-578 and 1-578 deleted for sequence 268 to 452) are associated with an IRES activity. These results were confirmed in a dicistronic context where the beta-galactosidase translation could be achieved only in the presence of a functional IRES. As mentioned on page 25 lines 17-22, betagalactosidase expression was indeed detected following translation of RNAs synthesized from all the constructs containing either the full length REV-A sequence 1-578 or shorter versions ((pREV CB-55 265-578) and pREV CG-52 (1-578 deleted for sequence 268 to 452)). In addition, comparative assays demonstrate that the REV-A long and short versions (1-578, 265-578, and 452-578) are capable of promoting beta-galactosidase synthesis more efficiently than the conventional EMCV IRES (see on page 25 lines 23-28).

Example 2 describes the construction of a series of retroviral vectors equipped with either REV-A 265-578 or 452-578 sequences inserted between two reporter genes plap and neo respectively. The retroviral vectors possess either MoMLV type LTRs (pREV HW vector series illustrated in Fig 3) or spleen necrosis virus (SNV) type LTRs (pMC vector series). In

addition, the numbered 1 and 4 vectors of each series is devoid of any encapsidation region whereas the numbered 2 and 5 constructs contain the VL30 encapsidation region and the numbered 3 and 6 constructs contain the MoMLV one. Titer measurement demonstrates that the 265-578 REV-A sequence is capable alone of promoting encapsidation of a SNV-based vector even when positioned in a non favorable location (*i.e.* between the two cistrons instead of immediately downstream of the viral LTR). In addition, this sequence is also capable of cooperating with a conventional encapsidation region, thus enhancing the encapsidation of the viral RNAs into the viral capsids and consequently the viral titers. Expression data of the reporter gene neo, especially in the presence of rapamycine which abrogates the cap-dependent translation machinery, confirms the functionality of these IRES-containing REV-A sequences.

Example 3 demonstrates the capacity of the dicistronic vector pREV HW-3 to transduce and express the reporter genes in human primary tumor cells of neuroectodermal origin. Furthermore, it is demonstrated that gene expression is not affected by the differentiation state of these Dev cells.

In conclusion, the experimental data supplied in the present specification demonstrate the presence of an IRES site in the 5' leader of the REV-A genome RNA capable of promoting efficient translation initiation in a cap-independent manner of a downstream cistron. The minimal IRES sequence resides within a 129 bp fragment (nt 452-578) of the REV-A 5' leader since all functional REV-A sequences have in common this portion (*e.g.* 1-578, 265-578, 1-268/452-578 and 452-578). Furthermore, the REV-A sequence ranging from 265 to 578 also provides encapsidation of the viral RNAs.

Therefore, Applicants maintain that the specification provides a sufficient disclosure and that the claims are enabled, as amended herein.

Regarding claims 12-15 and 48-49, the Examiner stated that the claims encompass various components in various combinations within a retroviral vector are not limiting the components to be operatively linked in the recited order. In order to expedite prosecution in

the subject application and without acquiescing to the Examiner's rejection, Applicants have amended claims 12 and 48 so as to clarify that the recited components are operably linked in a functional manner.

In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have canceled claims 16 and 50 without prejudice or disclaimer of the subject matter recited therein.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 8-19, 25-28, 31-35, 38, 40-45, and 47-51 under 35 U.S.C. § 112, first paragraph.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 8-19, 25-29, 31-35, 38, 40-45 and 47-51 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection.

Regarding claims 8, 25, and 31 and their dependent claims, the Examiner contends that the phrase "from the site of initiation of transcription up to the initiation codon of the gag gene" is unclear. The Examiner requests clarification with respect to which site of initiation and which gag gene the invention relies upon. Applicants maintain that these terms are perfectly understandable by a skilled person in the retrovirus art and that these two elements can be easily identified when reading the sequence of a REV-A virus. Furthermore, the Examiner asserts that the metes and bounds of the claims can not be determined due to the recitation of the phrase "the DNA equivalent of said genomic RNA".

As described above, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claims 8 and 25 to recite an avian reticuloendotheliosis virus of type A (REV-A), and amended claims 8 and 25 to no longer recite "or from the DNA equivalent of said genomic RNA, wherein said nucleotide sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation codon of the gag gene" but instead

recite "wherein said nucleotide sequence comprises at least the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 452 and ending at nucleotide 578 or the DNA equivalent of said portion in which U nucleotides are replaced by T nucleotides", and Applicants have amended claim 31 to recite that the REV-A sequence allowing encapsidation of a retrovirus or a retroviral vector comprises at least the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 265 and ending at nucleotide 578 or the DNA equivalent of said portion in which U nucleotides are replaced by T nucleotides. Given these amendments, the present claims point out and distinctly claim subject matter which applicant regards as the invention.

Regarding claims 14, 29, 35, and 45, the Examiner states that it is unclear what is the connection between the limitations (i), (ii), and (iii) with the rest of the claim. In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended these claims in order to clarify that the IRES site comprises one of the portions (i), (ii) or (iii) of the sequence presented in SEQ ID NO: 2.

Regarding claim 15, the Examiner contends that the phrase "the IRES site comprises a nucleotide sequence identical to the sequence presented in sequence identified SEQ ID NO: 2 or the DNA equivalent of said sequence, starting at nucleotide 265 and ending at nucleotide 578" is unclear considering that SEQ ID NO: 2 includes nucleotides 1 to 578. In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended dependent claim 15 to clarify that the IRES site comprises the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 265 and ending at nucleotide 578, or the DNA equivalent of said sequence, in which U nucleotides are replaced by T nucleotides.

Regarding claim 49, the Examiner contends that the phrase "the IRES site comprises a nucleotide sequence identical to the sequence presented in sequence identified SEQ ID NO: 2 or the DNA equivalent of said sequence, starting at nucleotide 452 and ending at nucleotide 578" is unclear considering that SEQ ID NO: 2 includes nucleotides 1 to 578. In

order to expedite prosecution in the subject application and not acqui sce to the Examiner's rejection, Applicants have amended dependent claim 49 to to clarify that the IRES site comprises the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 452 and ending at nucleotide 578, or the DNA equivalent of said sequence, in which U nucleotides are replaced by T nucleotides.

Regarding claims 18, 19, and 40, the Examiner contends that there is insufficient antecedent basis for "viral vector", because claim 8 is directed to a vector, not a viral vector. Additionally, the Examiner contends that in claim 40 it is unclear what is encompassed by the phrase "a pharmaceutical composition prepared from said vector or viral particle". In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claims 18, 19 and 40 to replace the term "viral vector" with "vector", and claim 40 has been amended to no longer recite "a pharmaceutical composition prepared from said vector or viral particle".

The 35 U.S.C. § 112, second paragraph rejection of claim 50 is rendered moot in light of the cancellation of claim 50.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 8-19, 25-29, 31-35, 38, 40-45, and 47-51 under 35 U.S.C. § 112, second paragraph.

III. Rejections under 35 U.S.C. § 102(b)

Claim 8, 9, 18 and 19 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Dornburg (WO94/29437). Applicants respectfully traverse this rejection.

The presently claimed invention relates to vectors including a portion of a nucleotide sequence isolated from the 5' end of the genomic RNA of an avian reticuloendotheliosis virus of type A (REV-A), and methods of use thereof. The claimed vectors and methods recite specific nucleotide sequences.

The vector of claim 8 includes a nucleotide sequence isolated from the 5' end of the genomic RNA of an avian reticuloendotheliosis virus of type A (REV-A). The nucleotide

sequence includes at least the portion of the sequence pres nted in SEQ ID NO: 2 starting at nucleotide 452 and ending at nucleotide 578, or the DNA equivalent of said portion in which U nucleotides are replaced by T nucleotides.

The method of claim 25 includes introducing into a vector a nucleotide sequence isolated from the 5' end of the genomic RNA of an avian reticuloendotheliosis virus of type A (REV-A). The nucleotide sequence includes at least the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 452 and ending at nucleotide 578, or the DNA equivalent of said portion in which U nucleotides are replaced by T nucleotides.

The method of claim 31 includes introducing into a retrovirus or retroviral vector a nucleotide sequence isolated from the 5' end of the genomic RNA of an avian reticuloendotheliosis virus of type A (REV-A). The nucleotide sequence includes at least the portion of the sequence presented in SEQ ID NO: 2 starting at nucleotide 265 and ending at nucleotide 578, or the DNA equivalent of said portion in which U nucleotides are replaced by T nucleotides.

As stated by the Examiner, Domburg discloses the preparation of highly-efficient, self-inactivating, recombination-free, U3-free retroviral vectors or viral particles derived from spleen necrosis virus (a reticuloendotheliosis virus) comprising part of the region of the 5' leader of the spleen necrosis virus which extends from a first nucleotide at the boundary between U3 and R to the initial codon of the gag gene. Dornburg does not describe vectors, or methods of use, as presently claimed. Dornburg does not describe nucleotide sequences isolated from the 5' end of the genomic RNA of an avian reticuloendotheliosis virus of type A (REV-A), as recited by the present claims. Further, Dornburg does not describe the specific portions of SEQ ID NO: 2, as recited in the present claims.

The teachings of Dornburg do not meet the limitations recited in the present claims. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Jamesbury Corp. v. Litton Industrial Products, Inc., 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985).

Therefore, Applicants respectfully request withdrawal of the rejection of claims 8, 9, 18, and 19 under 35 U.S.C. § 102(b).

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned agent concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Sherry M. Cauty Reg. #51,534
for Teresa Stanek Rea
Registration No. 30,427

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703)836-6620

Date: December 23, 2003

I hereby certify that this correspondence is being filed by facsimile transmission to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450, to facsimile number 1.703.872.9306 on this date, December 23, 2003.

by Sandra B. Paye
Sandra B. Paye